REMARKS

Claims 39-53 and 56-79 were presented for examination. Claims 39-53 and 56-71 and 75-78 were rejected. Claims 54 and 55 were canceled in an earlier amendment. Claims 72-74 and 79 were objected to as depending from a rejected claim but are indicated to be allowable if rewritten in independent form. Claims 39, 41, 53, and 59 are amended to claim a more specific aspect of the invention. The amendment limits the nature of the aryl ring that R^4 can represent. The limitation to "one heteroatom" is supported by the previous claim scope, which recited "one or more heteroatoms", as it merely deletes specific alternatives already disclosed. Claim 75 was canceled. Claim 76 was rewritten in independent form including all of the limitations of claim 75 from which it previously depended, and it was amended to more precisely track the language in claim 75 with regard to specific embodiments. These amendments add no new matter. Reconsideration in light of the following remarks is respectfully requested.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 39 and 75-78 were rejected as allegedly indefinite. According to the Office, the description of R^4 as "alkyl and aryl optionally including one or more heteroatoms selected from O, S and N" is indefinite and unclear.

The applicant traverses this rejection for at least the following reasons. In the previous response, the applicant provided a declaration from one of the inventors. The declaration states:

> From my own experience as a practicing organic chemist, I state that the phrase "optionally including one or more heteroatoms" would be understood to mean that the optional heteroatoms referred to can replace a carbon atom in the backbone or skeleton of the named alkyl or aryl group. The phrase would not be understood to refer to an appended heteroatom, which would be considered a 'substituent'.

The declaration further says:

> I further state that in the specific context of the present claims, where the groups described as "including one or more heteroatoms" are also described as optionally substituted by specifically named substituents, the phrase "including one or more

heteroatoms" could not reasonably be understood to describe heteroatoms other than those included within the backbone of the named hydrocarbon group. The separate description of the optional substituents would cover any heteroatoms attached to that backbone group.

The declaration further states:

I further state that a description of alkyl groups in the specification leads to the same conclusion. The specification says, "The alkyl or substituted alkyl may optionally include one or more heteroatoms which can be O, N or S, preferably N and O." The separation of 'alkyl' and 'substituted alkyl' distinguishes two types of alkyl groups, one with substituents and one without. The phrase "optionally including one or more heteroatoms," which is used to further describe these alkyl groups, can only reasonably be understood to describe variations of these groups other than substitutions. Thus the 'optionally included' heteroatoms must be heteroatoms that are permitted to replace carbon atoms within the backbone or skeleton of the alkyl groups being described.

The Office dismissed this declaration, saying "Such declaration further support the ambiguity of the terms and the propriety of the rejection. Were the structure limited to alkyl including heteroatoms replacing a carbon atom of the backbone, then, the particularity of such structure has not been pointed out as described by the declaration. Further, no antecedent basis for such description can be found in the specification."

Respectfully, the application describes the invention using terms that were commonly used and understood in the art; the declaration says that is the case. It is unclear how a declaration stating that a claim term has a clear meaning, and stating what one of ordinary skill would understand the term to mean, could be interpreted as evidence of ambiguity. The declaration is unrebutted evidence that one of ordinary skill would have understood these terms, and evidence of how they would have been interpreted by one of ordinary skill.

The Office further alleges that "the particularity of such structure has not been pointed out as described by the declaration."

It is true that the declaration uses *different words* from the ones in the claim to explain the claim terms, but of course the purpose of the declaration is to provide evidence that one of ordinary skill would have understood the words that are in the claims to have a clear meaning. And it does that: it demonstrates that the terms of the claim had a clear meaning. The declaration does not add to or change what is in the claims, it explains the challenged term in different words to confirm the clarity of the claim. The declaration is unrebutted evidence that the terms used in the claim had a clear meaning and did not need further explanation.

As pointed out before, the Office issued a patent using the same claim language in the claims of a related application with the same disclosure. Claim 1 of US 6,589,954 includes the phrase, "each of said alkyl and aryl optionally including one or more heteroatoms selected from O, S, and N", as do several of the other claims. That, too, is evidence that the claim language would have been understood by one of ordinary skill, and is thus not indefinite.

The preceding evidence was dismissed by the Office in the prior response without rebuttal: the Office only offered a hypothetical interpretation that is clearly inconsistent with the language in the specification and with the evidence of record in the declaration. Such a hypothetical is argumentation that is overcome by the evidence provided. Respectfully, unless the Office can provide rebuttal evidence to show that the claim language is indefinite, this rejection should be withdrawn.

The Office also says, "Further, no antecedent basis for such description can be found in the specification." The applicant does not understand any existing need to have or to show 'antecedent basis' and is thus unable to respond to this comment.

Claims 75-78, according to the Office, are confusing. One specific item noted by the Office that could be inconsistent was the inclusion of the phrase 'heart and brain failure (stroke) that are characterized by ischemia and reperfusion injury' in claim 75, and the allegedly broader term 'ischemic/reperfusion injury' in dependent claim 76. Accordingly, claim 76 has been amended to

include the same term used in claim 75. The amendment is supported by the language in existing claim 75 (now canceled), and resolves any possible antecedent basis issue.

The Office also seems to indicate that claim 78 is improperly dependent from claim 77. The Office said:

> Claim 77 is drawn to a method of treating condition associated with cardiac failure. In the dependent claim 78, said heart condition was limited to '...vasculitis, vascular restenosis, valvular disease...'. The definition of heart failure and vaculitis [sic] from the Merck Manual is hereby attached. Please note that none of the condition for heart failure included vasculitis and vasculitis is normally known as a blood vessel disease. Please note that clinically, proinflammatory response is not inflammation (see Cecil textbook of medicine, disorders of inflammatory response recited in PTO-892 07/26/04). The scope of the claims are [sic] very confusing. The above delineation are mere examples of the self conflicting scope of the claims and not an exhausted [sic] listing. Applicants are urged to consult medical textbooks, Merck manuals etc. for definition of diseases/pathology and clearly delineate what has been described and what conditions are further limitation of broad terms.

The applicant interprets this as a rejection for improper dependency of claim 77 from claim 78, apparently because the Office alleges that vasculitis cannot be "a heart condition associated with cardiac failure." However, the document describing heart failure that was provided by the Office in support of this rejection says, "Any disorder that directly affects the heart can lead to heart failure." (The document provided does not include the full text of the article the Office relied on: the right side is cut off, and there are no page numbers. This quote, though, is from the first line in the section entitled CAUSES.) Not surprisingly, a disease of the blood vessels such as vasculitis can affect the heart, as demonstrated by an article attached as Exhibit A, entitled "*Cardiac Vasculitis in Henoch-Schönlein Purpura.*" (**Exhibit A**: *Circulation 2000*: 101, e69-e70, available online at http://circulationaha.org.). This article describes the case of a 63 year old man whose heart and other systems failed, and whose autopsy showed vasculitis in the atrium of his heart. This demonstrates that vasculitis, as a condition associated with blood vessels, can damage the heart. As the Office's reference says, any condition that directly affects the heart can lead to heart failure. Accordingly, it is believed that 'vasculitis' in claim 78 is properly dependent from the term 'heart condition associated with heart failure' recited in claim 77.

The applicant appreciates the invitation to 'consult medical textbooks', and has responded to each stated basis for rejection. Each of the specific grounds for rejection has clearly been overcome, and no other issues are apparent to the applicant; accordingly the applicant respectfully requests that this rejection be withdrawn.

Rejections under 35 U.S.C. § 112, First Paragraph

'New Matter' Rejection

The Office rejected claims 39-71 and 75-78 for failure to comply with the written description and enablement requirements. The Office then alleges that certain claim amendments introduced "NEW MATTER". Claim 39 was previously amended to delete SO_2 from the recitation of alternatives that X^2 could represent. According to the Office, "that particular subgeneric scope as now claimed lacks antecedent basis in the specification. Further based on the description of page 5, line 14,that 'X^2 may be any of the alternatives set forth for X^1', the particular amendment specifically set forth a subset of combination of the two Markush elements is a teaching away from the description f the specification." Accordingly, per the Office, "Removal of NEW MATTER is required. In re Rasmussen 210 USPQ 325." [sic: this should be 211 USPQ 323 (CCPA 1981).]

First, the Office appears to be rejecting the claim based on a narrowing amendment, merely because the narrowing amendment does not find literal support in the specification. That is not at all the teaching of the cited case, which has nothing to do with a narrowing amendment. In re Rasmussen stands for the proposition that claim amendments are dealt with under 35 USC § 112 rather than under 35 USC § 132. It also demonstrates that an applicant is entitled to claim as much or as little of his invention as the prior art and disclosure will allow, and is not required to find literal support in the disclosure for a precise embodiment claimed. Rather, the court in that case allowed an applicant to amend a claim to use the phrase "adheringly applying", even though that term was not literally present in the specification, saying: "The phrase "adheringly applying" being supported in the specification, rejection of that claim under 35 U.S.C. 132, first paragraph, is *reversed*. Rejection under the appropriate statutory provision, 35 USC 112, would have been inappropriate." Clearly the In re Rasmussen court did not require literal antecedent basis for the challenged term, only 'support'.

In a similar case, where an applicant amended to delete certain embodiments from a claim to avoid a reference, the court said:

> While the board found that "no antecedent basis exists in the parent case" for the "limited genus" in claim 1, we see more than ample basis for claims of such scope. The 1963 disclosure is clearly directed to polymers of the type claimed. Fifty specific choices are mentioned for the E precursor compound, a broad *class* is identified as embracing suitable *choices* for the E' precursor compound, and twenty-six "examples" are disclosed which detail fifteen species of polyarylene polyethers. Only fourteen of those species and twenty-three of the "examples" are within the scope of the claims now on appeal. Two of the many choices for E and E' precursor compounds are deleted from the protection sought, because appellant is *claiming less* than the full scope of his disclosure. But, as we said in In re Wertheim, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976):
>
> Inventions are constantly made which turn out not to be patentable, and applicants frequently discover during the course of prosecution that only a part of what they invented and originally claimed is patentable.

In re Johnson, 194 USPQ 187, 195 (CCPA 1977).

While explaining its holding that an amended claim satisfied 35 USC § 112 without finding literal support in the application, the court in In re Johnson also said:

> The notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous species therewithin, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of §112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute. All that happened here is that appellants narrowed their claims to avoid having them read on a lost interference count.

Id. at 196.

Here, there is noting within the scope of the present claim that was not present in the claim prior to amendment. The claims were narrowed by deleting one possible alternative for the structural feature X^2: no new or unsupported descriptive matter was added, and no new claim scope was embraced. The present genus is fully supported by and consistent with the many examples in

the application. The applicant believes that this rejection is based on what the court described as "a hypertechnical application" of the statute, and requests that the Office withdraw the rejection.

Enablement Rejections

The Office organized an enablement rejection using certain of the *Wands* factors; accordingly, the following discussion is organized using the same headings used by the Office to make it easier to correlate with the text of the Office Action.

Nature of invention

The Office applies a *Wands* analysis to impose a rejection based on alleged lack of written description and enablement. That analysis begins with the explanation that the Office considers R^4 to be inadequately described. This issue was addressed above: the description of R^4 as "optionally including one or more heteroatoms selected from O, S and N" was shown to be clear to the reader of ordinary skill. Accordingly, it is not indefinite. Applying the correct standard merely give the claim term the broadest reasonable interpretation in light of the specification, as it would have been understood by one of ordinary skill. "The broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach. *In re Cortright*, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999)." MPEP 2111. Accordingly, the claim term should be interpreted in a manner consistent with the declaration.

The Office alleges:

> The method of treating disease as currently amended in claims 75-78 contains incredible utility. That is for a single compound to be able to treat such diversity of diseases as named in claim 75 is incredible. No nexus was found between the compound and such vast array of diseases nor was any nexus evidenced by the art that method of treating the claimed disease such as heart failure includes P38 kinase inhibitors (see Merck manual on drug fro treating heart failure.

First, claim 75, which recited a longer list of specific conditions, has been canceled. The remaining method claims recite a shorter list of specific conditions and are believed to be fully supported. The specification provides a clear nexus between the compounds of the claims and the utilities in the remaining claims. It relies on art-recognized connections disclosed in WO 98/28292,

WO 98/06715, WO 98/07425, and WO 96/40143 between inhibition of p38 kinase and the named conditions, which are characterized by their common connection to proinflammatory responses due to excessive activity of p38. Where a single biochemical path is known to be involved in a condition such as proinflammatory response that can take many forms and occur in various tissues, it is entirely credible scientifically that a compound that affects such a ubiquitous pathway can provide treatment for those various conditions.

The Office seems to suggest that p38 inhibitors cannot be accepted as useful to treat heart disease because the Merck manual does not say that they can: but applying that standard would ensure that no p38 compound *ever* made it into the Merck manual, because it demands evidence of a developed and registered drug as the threshold for patentability. The standard is also inconsistent with case law: MPEP 2164.02 indicates that *in vivo* activity can be adequately supported by *in vitro* data where the *in vitro* activity is known in the art to correlate with *in vivo* effects. See MPEP 2164.02 ("...if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).") Accordingly, the references provided in the application support the conclusion that the p38 inhibitors should be useful for the conditions in the claims.

The state of the art and predictability

The Office alleges that the area of chemistry involved is especially unpredictable, as part of the *Wands* analysis related to predictability. According to the Office,

> it is evidenced that when R4 is aryl including four nitrogen, the compounds have activity in treating proliferative disease (CA 139:117268). When the substituents on the bicylic ring wherein R4 is hydrogen, X1 is sulfonyl (CA 131:67650), the compounds have thrombin inhibition activity. Therefore, the drastic diversity in utility resulted from small chemical structure all falling within the claimed scope indicated the high degree of unpredictability of such compounds."

The Office then asserts:

> "Function of cytokine has been recognized in the art to be highly complexed [sic] and there is only limited understanding of the mechanism that lead to one activity over another when a specific cytokine is involved in a specific biological reaction (see CA 125:31527) that is no generalization can be extrapolated from such mechanism. In absence of any linkage of the particular enzyme inhibiting activity inexorably with any specific physiological function, the specification provided insufficient description to the currently amended scope.

First, as the applicant pointed out in response to the previous Office Action where similar statements were made about the unpredictability of this area of chemistry, it is not uncommon for a single compound to have multiple activities. As those of ordinary skill are well aware, a single compound can have multiple utilities, and compounds within a genus frequently have multiple effects. The citations provided by the Office do not suggest or demonstrate that even the compounds that the Office cites lack p38 activity; and those compounds are not within the scope of the claims anyway. Thus they are simply not related to a question of whether the compounds of the present genus are 'unpredictable'. They do not affect the credibility of the claims to biological activities that are based on demonstrated intrinsic activity and a known correlation between that *in vitro* activity and the *in vivo* activities of the claims. It is not clear why there could be any connection between the predictability of p38 activity and the possibility that a compound of similar structure might have a different or additional physiological effect.

The complexity of cytokine regulation, which the Office also mentions, is not indicative of the predictability of binding of compounds in the claimed genus to p38. The Office has offered no reasoning or evidence to suggest that the complexity of the cytokine pathway makes it difficult to predict that the claimed compounds will be inhibitors of p38, or that inhibition of p38 will have relevant physiological effects as it is reported to do. An applicant is not required to understand every detail of an underlying mechanism in order to claim an invention, as the Office will be aware.

Second, the Office's assertions are partly based on inaccurate information: X^1 cannot be sulfonyl within the scope of the claims. According to each of the independent claims that recites the compound genus, X^1 is CO, SO or CHOH. Sulfonyl is 'SO_2', and is not within the scope of the

claims. Accordingly, CA 131:67650 is irrelevant to the current claims. Furthermore, in view of the present amendment, CA 139:117268 is not within the scope of the claims, either. As amended, the claims do not read on a compound having multiple heteroatoms in an aryl group that would seem to correspond to R^4 in claim 39. The amendment clearly distinguishes the claims from the compounds disclosed in the cited reference. Thus these two observations are not instructive about the present claims.

Third, the Office appears to impose a special requirement in this case for data that "inexorably" links the demonstrated *in vitro* activity to a specific physiological effect. Quoting MPEP 2164.02:

> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):
>
> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence.

As this shows, 'a rigorous or an invariable exact correlation is not required': 'inexorable' is an inappropriate standard. If the correlation is disclosed and accepted in the art, it should be sufficient to meet the proper legal standards according to the courts and the MPEP. The Office's argument that this area is somehow particularly unpredictable was based on compounds that are clearly not within the claim scope, and is thus insufficient to meet the burden to show that the proven *in vitro* p38 activity of the compounds disclosed would not provide the claimed *in vivo* effects that are supported by the correlation of p38 activity to *in vivo* activities described in the cited references.

The Office then asserts:

> In so far as the method of treating disorder of the claims is concerned, it is well known in the art for treating eye inflammation i.e. uveitis, the ordinary route of

> administration is topical. For treating CNS disorders such as cerebral malaria, the drug must pass through the blood brain barrier. No description on [sic] dosage or site of administration for such diversity of method as found in claims 75-78 finds description or enabling evidence in the specification.

Respectfully, the application does provide descriptions of general methods for using the compounds of the claims at page 21, line 14 to page 22, line 26: it mentions topical, oral and transmucosal delivery methods, and a range of suitable dosages. It also cites Remington's Pharmaceutical Sciences as a source of detailed information for these matters, which is a resource that is routinely relied on in the art. Determining the precise mode and dosage for a particular indication are within the ordinary skill, as the Office's statement suggests: in that aspect, the level of skill is typically that of a treating physician, so it is quite high. As the Office is aware, "A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984)." MPEP 2164.01. Accordingly, the detail provided in the specification regarding modes of administration is believed to be sufficient.

The amount of guidance and working examples

According to the Office,

> A survey of the specification revealed that none of the X1 is sulfonyl compounds has been made or tested to have p38 activity. None of the compounds wherein R4 is broadly "aryl" including heteroatoms has been made or tested to have p38 activity.

Respectfully, the applicant points out that X^1 = sulfonyl is not within the scope of the claims. Accordingly, the observation related to it is irrelevant to the claims. The observation that one type of R^4 group is not specifically exemplified is equally irrelevant to the legal standard that should be applied: the issue is the amount of guidance provided, *not* whether a gap exists. The application discloses over 40 pages of synthesis and testing examples, including generally applicable synthesis methods, and data demonstrating both activity on p38 and selectivity for p38 over other kinases. The Office should consider the extensive guidance and enablement provided,

instead of looking for a gap that is not representative of the invention as a whole. Accordingly, the Office has not provided evidence that guidance provided by the specification is deficient based on the applicable legal standards.

Based on the above analysis, the Office concludes this *Wands* analysis section as follows:

> In view of the diversity of utility based on the bicyclic core with distinct substitution as evidenced supra, the lacking of variation for the Markush scope with such breadth finds the claimed scope lacks description as well as enablement. Especially, it is unclear of what is the claimed scope as delineated under the rejection under 35 USC 112 2nd paragraph supra.
>
> In addition, were applicants' proinflammatory response including diseases such as arthritis, a 102(f) or (g) issue may have to be resolved with the CA 139:117268 (see citation of PTO-892 07/26/04.)

As has been shown, the Office's preceding arguments are based in part on information related to compounds not within the scope of the claims. The alleged indefiniteness argument related to the description of R^4 was also rebutted. In other aspects, the reasoning and evidence asserted do not meet the burden on the Office to establish a rejection, as shown above. Accordingly, the enablement rejection is believed to be overcome, and the applicant respectfully requests that it be withdrawn.

5. Claims 39-53 and 58 (the Office Action indicates claims 1-58, but claims 1-38 and 54-55 were previously canceled) and 75-78 were provisionally rejected under 35 U.S.C. 102(e) based on Daun, US2005/0124649. The Office asserts that the instant application "discloses no compounds wherein R4 is aryl optionally including one or more heteroatoms selected from O, S and N. Therefore, the Daun et al. reference which disclosed heteroaryl moiety compounds anti-dated [sic] the instant specification and constituted a provisional 102(e)...which anticipated the instant claims for treating inflammatory and proliferative diseases."

The applicant has amended the claims to allow R^4, when it represents aryl, to contain at most one optionally included heteroatom. That clearly distinguishes all compounds of Daun that the

Office pointed out, each of which--like the generic structures that Daun discloses--includes a bicyclic imidazopyridyl group having at least three ring nitrogens in the only group that could correspond to R^4. Moreover, this rejection should not have been directed at claims 44, or the claims such as 46, 48, 50, 52 and 53 depending from it, because none of the compounds in the cited reference discloses X^1 = CO and X^2 = CH_2 as required by claim 44. Accordingly, this rejection should not have been applied to at least those claims, and it can be withdrawn as applied to all claims in view of the amendment.

6. The Office rejected claims 39-53 and 58 (the Office Action says claims 1-58, but claims 1-38 and 54-55 were previously canceled) under 35 U.S.C. 102(a) and (b) "as being clearly anticipated by Dominguez et al. CA 131:67650, Cook et al. CA 132:347492. See CA 131:67650 RN 228552-27-0, CA 132:347492 RN268730-34-3."

The applicant appreciates the copies of the cited structures that were provided by the Office, and traverses this rejection. As the Office is aware, an anticipation rejection can only be sustained if every claim limitation of the challenged claim is exactly present in a prior art reference. The claims clearly do not read on the species identified by the Office: the species RN 228552-27-0 could only align with the generic of claim 39 et seq. if X^1 were SO_2 (sulfonyl). As the applicant has pointed out in this and previous responses, this reference cannot anticipate any claim of this application because no claim includes compounds wherein X^1 is SO_2. Accordingly, the anticipation rejection based on Dominguez should be withdrawn.

Similarly, the claims clearly do not read on the species identified by the Office in the Cook reference. The compound identified by the Office cannot map onto or align with the generic structure of claims 39 et seq. unless X^2 is NH. The cited reference cannot anticipate any claim of this application, because no claim includes compounds wherein X^2 is NH. Accordingly, this anticipation rejection based on Cook can be withdrawn.

The Office also states that "the rejection of the previous office action is maintained when the new matter is removed from the claims and the claims are reversed to the previous version containing structure of 'isosteres' of CO or CH_2."

This appears to be based on the 'New Matter' rejection discussed above. As the Office will be aware in view of the previous discussion of In re Johnson, the applicant is not required to recite in the claims all of the subject matter to which the applicant is entitled, and the claims do not have to find literal support in the application, as long as they are supported by it. The claims as amended are fully supported by the specification and its long section of examples. Accordingly, the rejection of the previous office action was overcome by that previous amendment and need not be reasserted.

7. The Office rejected claims 39-53 and 58 (the Office Action indicates claims 1-58, but claims 1-38 and 54-55 were previously canceled) under 35 U.S.C. § 103(a) over Dominguez, Cook, or Kalihana (CA 135:313624) in view of King or Patani, two references that relate to the general concepts of bioisosterism.

According to the Office, the following is related to a 'determination of the scope and content of the prior art':

> The primary references disclosed structurally analogous compounds, see CA 131:67650 RN 228552-27-0, CA132:347492 RN268730-34-3 or CA 135:313624 RN 367508-34-7, 367509-01-1, 367510-05-2 i.e. RN 367509-01-1 position isomer being taught by RN 36750803407 or RN 367510-05-2 that changing position is obvious.

As a preliminary point, all compounds of Kalihana as provided by the Office are clearly distinguishable from the present claims. None of the compounds the Office identified in Kalahana resemble the claimed structures in any significant way. Only one of the specific compounds from that reference has a bicyclic aromatic system with a nitrogen in its five membered ring, as required by the claims; and that compound has no substituent at all on its 6-membered ring. Furthermore, it

includes no group that can correspond to R^1 as claimed and no feature that corresponds to X^2 of the claimed invention. Accordingly, Kalahana cannot serve as a basis for an obviousness rejection.

The Office further asserts:

> The difference between the delineated compounds supra is that instead of X1 is CO, SO or CHOH and X2 is CH, CH_2, CO, CHON[sic], SO or SO_2, the prior are compounds contain X1 or X2 being isostere of the claimed structure. King disclosed variations of isosteric linker for CO or CH2 being SO or NH, while Patani et al. provided motivation that isosteric modification of a known compound is the rational approach for drug design.
>
> One having ordinary skill in the art is deemed to be aware of all the pertinent art in the field. The above references places the proven compounds and the rational approach in modification in the possession of artisan in the field. One having ordinary skill in the art would be motivated to modify the prior art compounds with the known isosteric replacement of the linkers **because** such modification is rational and is expected to produce more useful drugs for a lead compound.

The applicant traverses this rejection for at least the following reasons.

First, no *prima facie* case for an obviousness rejection was established. A proper obviousness rejection requires a particularized explanation for the basis for alleging obviousness. According to MPEP 2142: "A statement of a rejection that includes a large number of rejections must explain with reasonable specificity at least one rejection, otherwise the examiner procedurally fails to establish a *prima facie* case of obviousness. *Ex parte Blanc*, 13 USPQ2d 1383 (Bd. Pat. App. & Inter. 1989)." In this case, the Office cited numerous compounds and multiple differences that distinguish them from the claims, and only broad statements about how they allegedly support a finding of obviousness. No example or explanation of a specific basis for a rejection was provided. Regardless of whether any particular modification of any specific compound would be rational to try based on possible bioisosterism, the Office does not establish a *prima facie* rejection without providing a specific description of the basis for one according to *Ex parte Blanc.* Under the standard in that case, no *prima facie* case for an obviousness rejection was established.

Furthermore, the Office did not meet the burden required to demonstrate that one of ordinary skill would have combined the references in any particular way. Assuming arguendo that the references can be combined or modified, saying that such combination is 'rational' is insufficient motivation for the modification of a reference. The rejection as provided amounts to an 'obvious to try' standard, in a situation where there are numerous options or directions available and no guidance toward any particular one. Such rejections have been soundly rejected by the courts. (In re O'Farrell, 7 USPQ2d 1673: "The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. *E.g .*, *In re Geiger* , 815 F.2d at 688, 2 USPQ2d at 1278; *Novo Industri A/S v. Travenol Laboratories, Inc .*, 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); *In re Yates* , 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); *In re Antonie* , 559 F.2d at 621, 195 USPQ at 8-9.") That is precisely the situation in this case.

The references provided by the Office provide numerous examples of groups that are said at least in some situations to behave as though they are bioisosteric. Such groups include single atoms (Table 1 of Patani) and multiple examples of bivalent, trivalent, ring, and carbonyl bioisosteric replacement possibilities. (See the Tables in King.) This provides a great many ways to modify any compound in the cited references. The result of viewing any single compound of the cited references in view of the MANY options for modifications leads to an incomprehensible number of options that could lead the person of ordinary skill in countless different directions. There is no indication that the references would have provided guidance toward or away from any one of the seemingly endless alternative paths. Accordingly, under the standard summarized for similar situations in In re Farrell, the burden of showing motivation to modify the teachings of the cited references to establish an obviousness rejection was not met, without guidance from the references toward a specific modification or combination.

The Office has not pointed to one compound in a reference to indicate why that particular compound would have been selected, or shown why one of ordinary skill would have modified it in the specific fashion required to render obvious a compound within the present claims. Accordingly, the person of ordinary skill could not have arrived at a compound within the present claims based on the broad array of options: only using the applicant's disclosure as a road map could one arrive at the presently claimed invention from the cited references. As the Office is no doubt aware, a hindsight analysis is improper in an obviousness rejection. Accordingly, this rejection can properly be withdrawn.

Moreover, the references provided by the Office also clearly show that bioisosterism is fraught with unpredictability. An obviousness analysis requires the Office to demonstrate a 'reasonable expectation of success.' However, the references say that the bioisosterism approach does not provide that level of predictability. According to King, at pg. 209:

> When considering any approach to lead optimization, alteration of one part of the molecule almost always affects more than just one property. Isosteric and bioisosteric replacements are no exception and this should always be considered with analyzing the result of such replacements. For example a simple CH_2 to O to S series of replacements can alter size, shape, electronic distribution, water or lipid solubility, pKa, metabolism, or hydrogen bonding capacity, **all with unpredictable effects upon biological activity**. (emphasis added)

One of ordinary skill would be well aware of this caveat in applying bioisosterism to modification of a biologically active compound. Therefore, one of ordinary skill would at most have a *hope* of success in making any particular bioisosteric replacement; and would have no particular reason to choose one that would lead in a direction that would affect the current claims. The possibility that one feature of a molecule could be replaced with a 'known bioisostere' *at most* makes it logical or 'rational' to try the replacement: as the reference states, it does not allow one to predict the biological activity of the product. Accordingly, the Office has not met the burden of demonstrating that modifying a compound based on the concepts of bioisosterism would provide a reasonable expectation of success in providing a biologically active compound, and this obviousness rejection can be withdrawn.

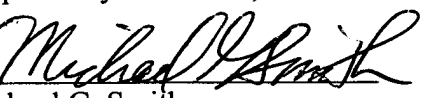
Finally, in rejecting the compound claims, the Office has provided no specific basis to reject a *single one of the dependent claims* having any generic scope. Claims 40-53 and 56-71 narrow the scope of the claims to successively smaller subgenera. Nevertheless, many of the rejections were applied to all compound claims except those that name the specific compounds disclosed. In effect, this approach to examination improperly limits the claims to the exemplified compounds named in claims 72-74. Accordingly, the dependent claims should not have been summarily rejected without individual analysis.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Office is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Office is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 219002028310. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: March 13, 2006

Respectfully submitted,

By 

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